HIV Drug Resistance in Adults Failing Early Antiretroviral Treatment: Results From the HIV Prevention Trials Network 052 Trial

Jessica M. Fogel, PhD,[1] Sarah E. Hudelson, BS,[1] San-San Ou, MS,[2] Stephen Hart, PhD,[3] Carole Wallis, PhD,[4] Mariza G. Morgado, PhD,[5] Shanmugam Saravanan, PhD,[6] Srikanth Tripathy, MD,[7] Laura Hovind, MS,[3] Estelle Piwowar-Manning, BS, MT (ASCP),[1] Devin Sabin, MS,[1] Marybeth McCauley, MPH,[8] Theresa Gamble, PhD,[9] Xinyi C. Zhang, PhD,[2] Joseph J. Eron, MD,[10] Joel E. Gallant, MD, MPH,[11] Johnstone Kumwenda, FRCP,[12] Joseph Makhema, MBChB, FRCP,[13] Nagalingeswaran Kumarasamy, MBBS, PhD,[14] Suwat Chariyalertsak, MD, DrPH,[15] James Hakim, MD,[16] Sharlaa Badal-Faesen, MBBCh,[17] Victor Akelo, MBChB, MPH,[18] Mina C. Hosseinipour, MD, MPH,[19,20] Breno R. Santos, MD,[21] Sheela V. Godbole, MD, PGDEPI,[22] Jose H. Pilotto, MD,[23] Beatriz Grinsztejn, MD, PhD,[24] Ravindre Panchia, MBBCh,[25] Kenneth H. Mayer, MD,[26,27] Ying Q. Chen, PhD,[28] Myron S. Cohen, MD,[10] and Susan H. Eshleman, MD, PhD[1]

Abstract: Early initiation of antiretroviral treatment (ART) reduces HIV transmission and has health benefits. HIV drug resistance can limit treatment options and compromise use of ART for HIV prevention. We evaluated drug resistance in 85 participants in the HIV Prevention Trials Network 052 trial who started ART at CD4 counts of 350–550 cells per cubic millimeter and failed ART by May 2011; 8.2% had baseline resistance and 35.3% had resistance at ART failure. High baseline viral load and less education were associated with emergence of resistance at ART failure. Resistance at ART failure was observed in 7 of 8 (87.5%) participants who started ART at lower CD4 cell counts.

Key Words: HIV, HPTN 052, early ART, ART failure, resistance

(*J Acquir Immune Defic Syndr* 2016;72:304–309)

INTRODUCTION

The multinational HIV Prevention Trials Network (HPTN) 052 trial showed that early initiation of antiretroviral treatment (ART) significantly reduces sexual HIV transmission in serodiscordant couples.[1,2] Early ART initiation has also been shown to have health benefits for the HIV-infected individual receiving treatment, including lower rates of severe illness[3–5] and increased survival.[6] In the United States, ART has been recommended for all HIV-infected individuals regardless of CD4 cell count since 2012.[7,8] The World Health Organization guidelines were recently changed to recommend ART for all HIV-infected individuals, regardless of CD4 cell count.[9]

Use of ART for HIV treatment and prevention can be compromised by HIV drug resistance, especially in resource-limited settings where resistance testing is not routinely performed as part of clinical management. There is relatively little information available about emergence of HIV drug resistance in individuals who initiate ART at higher CD4 cell counts. Observational studies in the United Kingdom and North America have reported a lower prevalence of treatment-emergent HIV drug resistance among patients who start ART early.[10–12] However, little is known about the factors associated with drug resistance in HIV-infected individuals who initiate ART at higher CD4 cell counts or in settings where ART is used for HIV prevention. In this study, we analyzed HIV drug resistance among HIV-infected individuals who failed ART in the HPTN 052 trial before the interim study report was released.

METHODS

Study Cohort

HPTN 052 (NCT00074581) was a phase 3, randomized, controlled clinical trial that enrolled HIV serodiscordant couples in Africa, Asia, and the Americas.[1–3] HIV-infected (index) participants had CD4 cell counts of 350–550 cells per cubic millimeter at enrollment. In the early ART arm, index participants initiated ART immediately after enrollment. In the delayed ART arm, index participants initiated ART when their CD4 cell count was <250 cells per cubic millimeter on 2 consecutive study visits or when they developed an AIDS-defining illness.[1] Viral load was measured quarterly.

Enrollment criteria for index participants included no previous antiretroviral (ARV) drug use, except for short-term regimens for prevention of mother-to-child transmission. Participants who had a viral load $\leq$400 copies per milliliter at enrollment were excluded from the analyses; some of those participants were found to be on ART at the time of enrollment but did not disclose this to study staff.[13] The most common ART regimen used was a combination of efavirenz, lamivudine, and zidovudine.[1] This report includes analysis of data from the start of the trial (June 2007) through May 2011 (interim report of the primary study outcome).

Laboratory Methods

HIV viral load and CD4 cell count were determined at study sites.[1] HIV genotyping was performed retrospectively using the ViroSeq HIV-1 Genotyping System, v2.8 (Celera Diagnostics, Alameda, CA). This testing was performed at 4 study sites (Pune and Chennai, India; Johannesburg, South Africa; Rio de Janeiro, Brazil) and at the HPTN Laboratory Center (Baltimore, MD, USA). Resistance results were calculated using the Resistance Calculator program at Frontier Science Foundation using the Stanford v6.3 algorithm.[14] Sequences were submitted to GenBank (accession numbers: KT833391-KT833560, KU562071-KU562085). HIV subtyping was performed by phylogenetic analysis. Laboratories that performed HIV genotyping participated in the US Division of AIDS Virology Quality Assurance program.[15] Laboratories that performed CD4 cell count testing participated in the United Kingdom National External Quality Assessment Service external quality assurance program.[16]

Statistical Analysis

Viral suppression was defined as the first of 2 consecutive viral load measurements $\leq$400 copies per milliliter after ART initiation. ART failure was defined as the first of 2 consecutive viral load measurements $>$1000 copies per milliliter after 24 weeks on ART. HIV drug resistance was assessed by testing samples collected at ART initiation (baseline) and ART failure. Demographic and clinical factors were analyzed for association using logistic regression. The association of baseline resistance with time to viral suppression after ART initiation was analyzed using Cox proportional hazards model. Analyses were performed using SAS software, v9.4 (SAS Institute, Cary, NC).

Ethical Considerations

Written informed consent was obtained from all participants in the HPTN 052 trial. The trial was approved by the institutional review boards/ethics committees at each participating institution.

Received for publication November 20, 2015; accepted February 1, 2016.

From the [1]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD; [2]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA; [3]Frontier Science & Technology Research Foundation, Amherst, NY; [4]Specialty Molecular Division, Lancet Laboratories and BARC-SA, Johannesburg, South Africa; [5]Laboratory of AIDS and Molecular Immunology, Oswaldo Cruz Institute, Rio de Janeiro, Brazil; [6]Y. R. Gaitonde Centre for AIDS Research and Education, Chennai, India; [7]National JALMA Institute for Leprosy and Other Mycobacterial Diseases, Agra, India; [8]Science Facilitation Department, FHI 360, Washington, DC; [9]Science Facilitation Department, FHI 360, Durham, NC; [10]Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC; [11]Southwest CARE Center, Santa Fe, NM; [12]College of Medicine-Johns Hopkins Project, Blantyre, Malawi; [13]Botswana Harvard AIDS Institute, Gaborone, Botswana; [14]YRGCARE Medical Centre, VHS, Chennai, India; [15]Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand; [16]Department of Medicine, University of Zimbabwe, Harare, Zimbabwe; [17]Wits Reproductive Health and HIV Institute, University of Witwatersrand, Johannesburg, South Africa; [18]Kenya Medical Research Institute, Center for Disease Control, Kisumu, Kenya; [19]Division of Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC; [20]UNC Project-Malawi, Institute for Global Health and Infectious Diseases, Lilongwe, Malawi; [21]Serviço de Infectologia, Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; [22]Department of Epidemiology and Biostatistics, National AIDS Research Institute (ICMR), Pune, India; [23]Hospital Geral de Nova Iguacu and Laboratorio de AIDS e Imunologia Molecular-IOC/Fiocruz, Rio de Janeiro, Brazil; [24]Instituto Nacional de Infectologia Evandro Chagas-INI-Fiocruz, Rio de Janeiro, Brazil; [25]Perinatal HIV Research Unit, University of the Witwatersrand, Soweto HPTN CRS, Soweto, South Africa; [26]Fenway Health and Infectious Disease Division, The Fenway Institute; [27]Beth Israel Deaconess Medical Center/Department of Medicine, Harvard Medical School, Boston, MA; and [28]Vaccine and Infectious Disease Division and Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA.

Supported by the grants from the Division of AIDS of the U.S. National Institute of Allergy and Infectious Diseases (NIAID); and by the Office of AIDS Research of the U.S. National Institutes of Health (NIH) [U01-AI068613/UM1-AI068613 (S.H.E.); U01-AI068617/UM1-AI068617 (Donnell); and U01-AI068619/UM1-AI068619 (Vermund/El-Sadr)]. Study drugs used in HPTN 052 were donated by Abbott Laboratories, Boehringer-Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb, Gilead Sciences, Inc., GlaxoSmithKline/ViiV Healthcare, and Merck & Co., Inc.

This article was submitted with the permission of the Director of Kenya Medical Research Institute (KEMRI). This work was presented in part at 8th IAS Conference on HIV Pathogenesis, Treatment & Prevention, July, 2015, Vancouver, Canada.

S.H.E. has collaborated with investigators from Abbott Diagnostics on research studies. J.J.E. is a consultant to Bristol Myers Squibb, Gilead Sciences, ViiV Healthcare and Merck; he receives research support from ViiV Healthcare and Janssen through contracts to the University of North Carolina. J.E.G. receives honoraria for advisory board and/or membership on Data Safety and Monitoring Boards from Bristol-Myers Squibb, Gilead Sciences, Janssen Therapeutics, Merck & Co., and ViiV Healthcare; his organization receives grant support from those companies as well as AbbVie and Sangamo Biosciences. C.W. served as a consultant for Celera for development of software updates related to the HIV drug resistance algorithm used with the ViroSeq HIV-1 Genotyping System. The remaining authors have no conflicts of interest to disclose.

All authors meet the journal's criteria for authorship. Individual contributions/author roles are listed below: J.M.F., analyzed the data, prepared the manuscript; S.E.H., performed HIV genotyping and analyzed study results; S.-S.O., statistical research associate for HPTN 052; S.H., analyzed HIV drug resistance data, performed HIV subtyping analysis; C.W., coordinated HIV genotyping for HPTN 052 sites in Africa; M.G.M., coordinated HIV genotyping for HPTN 052 sites in Brazil; S.S., coordinated HIV genotyping for HPTN 052 sites in Chennai, India, and Thailand; S.T., coordinated HIV genotyping for the HPTN 052 site in Pune, India; L.H, assisted with analysis of HIV genotyping data; E.P.-M., HPTN Laboratory Center Quality Assurance/Quality Control Coordinator for HPTN 052; D.S., performed HIV genotyping; M.M., Senior Study Manager for HPTN 052; T.G., Senior Study Manager for HPTN 052; X.C.Z., assisted with statistical analysis; J.E., HPTN 052 investigator; J.E.G., HPTN 052 investigator; J.K., HPTN 052 investigator, Blantyre, Malawi; J.M., HPTN 052 investigator, Gaborone, Botswana; N.K., HPTN 052 site PI, Chennai, India; S.C., HPTN 052 investigator, Chiang Mai, Thailand; J.H., HPTN 052 investigator, Harare, Zimbabwe; S.B.-F., HPTN 052 investigator, Johannesburg, South Africa; V.A., HPTN 052 investigator, Kisumu, Kenya; M.H., HPTN 052 investigator, Lilongwe, Malawi; B.R.S., HPTN 052 investigator, Porto Alegre RS, Brazil; S.V.G., HPTN 052 investigator, Pune, India; J.H.P., HPTN 052 site PI, HGNI, Rio de Janeiro, Brazil; B.G., HPTN 05 site PI, Fiocruz, Rio de Janeiro, Brazil; R.P., HPTN 052 site PI, Soweto, South Africa. K.H.M., HPTN 052 site PI, Boston, USA; Y.Q.C., Protocol Statistician for HPTN 052; M.S.C., Protocol Chair for HPTN 052; S.H.E., Virologist for HPTN 052, designed the study, analyzed the data, prepared the manuscript.

Correspondence to: Susan H. Eshleman, MD, PhD, Department of Pathology, The Johns Hopkins Medical Institutions, Ross Building, Room 646, 720 Rutland Avenue, Baltimore, MD 21205 (e-mail: seshlem@jhmi.edu).

RESULTS

Study Cohort

In HPTN 052, 886 index participants were randomized to the early ART arm; 95 (10.7%) of those participants failed ART by May 2011. Ten participants were excluded from analysis (2 had viral loads ≤400 copies/mL at enrollment and 8 did not have paired genotyping results from baseline and ART failure visits). The remaining 85 participants had a median follow-up of 1.99 years (range: 0.74–5.65) in the period assessed. The median baseline $\log_{10}$ viral load was 4.42 copies/mL (interquartile range: 3.76–4.86) and the median baseline CD4 cell count was 459.5 cells per cubic millimeter (interquartile range: 373–542.5). Most (39/42 = 92.9%) HIV infections at the African sites were subtype C; other infections included varied HIV subtypes with 1 to eight infections of each subtype (Table 1). Therefore, HIV subtype was not included in the analyses below. We did not observe an association between region (Africa, the Americas, and Asia) and resistance in any of the analyses described below.

In the delayed ART arm, 213 (24.0%) of 887 index participants started ART in this study and 9 failed ART by May 2011. Genotyping results were obtained for 7 of 9 participants at baseline and eight of those participants at ART failure (6 had paired baseline/failure results).

HIV Drug Resistance

In the early ART arm, 7 (8.2%) of the 85 participants who failed ART had drug resistance mutations detected at baseline

TABLE 1. Factors Associated With HIV Drug Resistance at Initiation of Antiretroviral Treatment (baseline) and at the Time of Treatment Failure*

		Resistance at Baseline			Resistance at ART Failure			New Resistance at ART Failure		
Variables	**Total**	**N (%)**	**Odds Ratio (95% CI)**	***P***	**N (%)**	**Odds Ratio (95% CI)**	***P***	**N (%)**	**Odds Ratio (95% CI)**	***P***
Age, yrs										
<25	12	2 (17)			6 (50)	ref		5 (42)	ref	
25–39	57	5 (9)			20 (35)	0.54 (0.15 to 1.90)	0.34	18 (32)	0.65 (0.18 to 2.32)	0.50
≥40	16	0 (0)			4 (25)	0.33 (0.07 to 1.65)	0.18	4 (25)	0.47 (0.09 to 2.34)	0.35
Sex										
Male	47	3 (6)	ref		17 (36)	ref		17 (36)	ref	
Female	38	4 (11)	1.73 (0.36 to 8.23)	0.49	13 (34)	0.92 (0.37 to 2.25)	0.85	10 (26)	0.63 (0.25 to 1.61)	0.33
Baseline CD4 cell count†	84	7 (8)	0.92 (0.47 to 1.80)	0.80	30 (35)	0.70 (0.46 to 1.05)	0.09	26 (31)	0.75 (0.49 to 1.13)	0.17
Baseline $\log_{10}$ viral load‡	85	7 (8)	0.65 (0.21 to 1.99)	0.45	30 (35)	2.36 (1.17 to 4.78)	**0.017**	27 (32)	3.02 (1.41 to 6.49)	**0.0046**
Region§										
Americas	14	2 (14)	ref		5 (36)	ref		5 (36)	ref	
Asia	29	2 (7)	0.44 (0.06 to 3.54)	0.44	10 (34)	0.95 (0.25 to 3.60)	0.94	10 (34)	0.95 (0.25 to 3.60)	0.94
Africa	42	3 (7)	0.46 (0.07 to 3.09)	0.43	15 (36)	1.00 (0.28 to 3.53)	1.00	12 (29)	0.72 (0.20 to 2.59)	0.62
Regimen‖										
EFV/3TC/ZDV	66	6 (9)	1.80 (0.20 to 15.9)	0.60	26 (39)	2.44 (0.73 to 8.16)	0.15	24 (36)	3.05 (0.81 to 11.5)	0.10
Other	19	1 (5)	ref		4 (21)	ref		3 (16)	ref	
Education										
None	16	2 (13)			10 (63)	ref		9 (56)	ref	
Primary or secondary schooling	65	5 (8)			19 (29)	0.25 (0.08 to 0.78)	**0.017**	17 (26)	0.28 (0.09 to 0.85)	**0.026**
Postsecondary schooling	4	0 (0)			1 (25)	0.20 (0.02 to 2.39)	0.20	1 (25)	0.26 (0.02 to 3.06)	0.28
Marital status										
Married	81	6 (7)	ref		28 (35)	ref		25 (31)	ref	
Not married	4	1 (25)	4.17 (0.37 to 46.4)	0.25	2 (50)	1.89 (0.25 to 14.2)	0.53	2 (50)	2.24 (0.30 to 16.8)	0.43
No. sex partners										
0–1	82	7 (9)			29 (35)	ref		26 (32)	ref	
>1	3	0 (0)			1 (33)	0.91 (0.08 to 10.5)	0.94	1 (33)	1.08 (0.09 to 12.4)	0.95
Baseline resistance										
Yes	7				7 (100)			4 (57)	3.19 (0.66 to 15.4)	0.15
No	78				23 (29)			23 (29)	ref	

$P < 0.05$ are bolded. Regression models could not be generated if any cell was 0 for the categorical variable.

*The analyses included the 85 HIV-infected index participants in the early ART arm of HPTN who failed ART (see text).

†Assessed as increments of 100 CD4-positive cells per cubic millimeter.

‡Assessed as increments of $\log_{10}$ viral load.

§The 85 participants had the following HIV subtypes: 69 (81.2%) subtype C (Malawi [N = 29], India [N = 28], Zimbabwe [N = 7], South Africa [N = 3], and Brazil [N = 2]), 8 subtype B (Brazil), 3 subtype F1 (Brazil), 1 subtype A2 (Kenya), 2 A1 (Kenya), 1 CRF1_AE (Thailand), and 1 CRF12_BF (Brazil).

‖Most participants who started ART on the EFV/3TC/ZDV regimen (with the exception of pregnant women) received a fixed-dose formulation of these drugs.

3TC, lamivudine; EFV, efavirenz; ref, reference group; ZDV, zidovudine.

(including 4 women, one of whom reported previous use of ARV drugs during pregnancy, Fig. 1). Three had nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance only, 1 had nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) resistance only, and 3 had both NNRTI and NRTI resistances. Thirty (35.3%) of the 85 participants had drug resistance mutations detected at ART failure; 19 had NNRTI resistance only, 3 had NRTI resistance only, and 8 had both NNRTI and NRTI resistances (Fig. 1). Twenty-seven (90.0%) of the 30 participants had resistance mutations detected at failure that were not present at baseline. Twenty-three had new NNRTI resistance; all had new resistance to efavirenz, and most had cross-resistance to other NNRTIs. Eight had new NRTI resistance; all had new resistance to lamivudine and emtricitabine; 1 also had new resistance to abacavir and didanosine. Protease inhibitor resistance was not observed in any samples.

In the delayed ART arm, baseline resistance was detected in 2 (28.6%) of 7 participants with genotyping results. At ART failure, 7 (87.5%) of 8 participants who had genotyping results had resistance, including all 6 participants with paired baseline/failure results. Both of the participants who had baseline resistance acquired new resistance at failure. The frequency of resistance at ART failure was significantly higher in the delayed ART arm compared with the early ART arm (7/8 [87.5%] vs. 30/85 [35.2%], $P = 0.006$, Fisher exact test).

Factors Associated With HIV Drug Resistance

Because only 9 participants in the delayed ART failed ART by the May 2011 arm, factors associated with HIV drug resistance were assessed in the early ART arm only. None of the clinical or demographic factors analyzed were associated with baseline drug resistance among those who failed ART (Table 1). A higher baseline viral load was associated with resistance at ART failure and with new resistance at ART failure. Having primary or secondary schooling (compared to no education/schooling) was associated with a lower frequency of resistance at ART failure and new resistance at ART failure. Baseline drug resistance was not associated with time to viral suppression after ART initiation among the 85 participants who failed ART; 50 (58.8%) of the 85 participants never achieved viral suppression before meeting the criteria for ART failure. There was no difference ($P = 0.2$, χ^2 test) in the frequency of new resistance at ART failure among those who never achieved viral suppression (15/50 = 30.0%), those who achieved viral suppression and remained virally suppressed before ART failure (10/28 = 35.7%), and those who achieved viral suppression but had intermittent viremia before ART failure (2/7 = 28.6%).

DISCUSSION

HIV drug resistance may compromise the use of ART for HIV treatment and prevention. ART is now recommended for all HIV-infected individuals, regardless of CD4 cell count.[7–9,17,18] However, few studies have evaluated HIV drug resistance when ART is initiated at higher CD4 cell counts. Among participants who failed ART in the early ART arm of HPTN 052 (data through May 2011), 8.2% had resistance at the time of ART initiation. This is similar to the frequency of baseline resistance among participants who failed ART in the ACTG 5175 study (Prospective Evaluation of Antiretrovirals in Resource-Limited Settings [PEARLS]), which enrolled participants at many of the same study sites as HPTN 052. In PEARLS, ART was initiated at lower CD4 cell counts (<300 cells/mm^3); the frequency of baseline resistance in PEARLS was 9.4% among those who

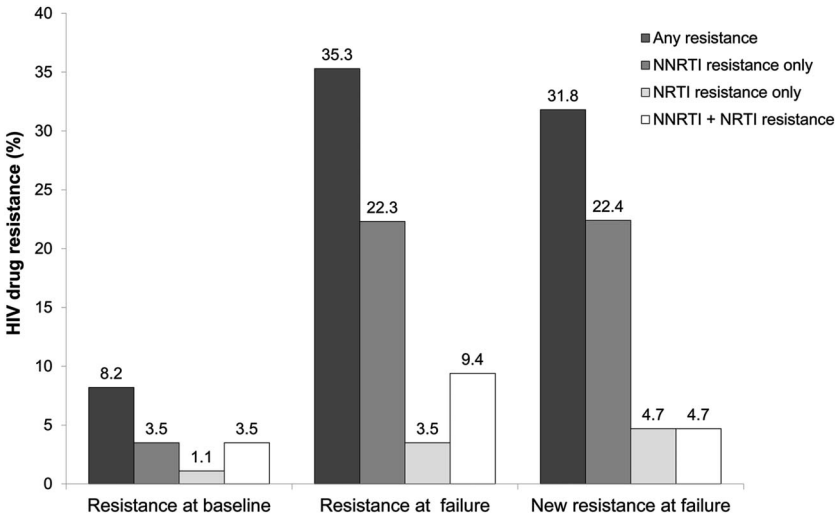

FIGURE 1. Proportion of participants with HIV drug resistance at baseline and at treatment failure. The figure shows the frequency of HIV drug resistance among participants in the early ART arm of HPTN 052 who failed ART (N = 85 with paired baseline/failure results). Seven (8.2%) participants had resistance at baseline. The most common NNRTI and NRTI mutations were Y181C and M184V, which were each detected in 3 of the 7 cases. All the mutations detected at baseline, with the exception of one Y181C mutation, were also present in the corresponding failure samples. Thirty (35.3%) had resistance at ART failure. The most common NNRTI mutation was K103N, which was detected in 20 (66.7%) of the 30 cases. The most common NRTI mutation was M184V, which was detected in 11 (36.7%) of the 30 cases. Twenty-seven (90.0%) of those 30 participants had one or more resistance mutations detected at failure that was not present at the time of ART initiation (K103N [n = 18], M184V [n = 8], V106M [n = 4], V108I [n = 2], K238T [n = 2], G190A [n = 1], and K101E [n = 1]). Twenty-three (85.2%) had new resistance to efavirenz, and most had cross-resistance to other NNRTIs (nevirapine [N = 21], rilpivirine [N = 2], and etravirine [N = 1]). Eight (29.6%) had new NRTI resistance; all had new resistance to lamivudine and emtricitabine; 1 also had new resistance to abacavir and didanosine because of the acquisition of M184V in addition to the baseline mutations M41L and T215E. Protease inhibitor resistance was not observed in any samples. Among the 78 (91.8%) participants who did not have baseline resistance, 23 (27.1%) had resistance at failure (not shown).

failed ART and 4.3% among those in a case–control group of those who did not fail ART.[19]

In HPTN 052, the frequency of resistance at ART failure was significantly lower in the early ART arm than in the delayed ART arm (35.3% vs. 87.5%, $P = 0.006$). It is important to note, however, that very few participants in the delayed ART arm failed ART by May 2011. In other studies where ART was initiated at lower CD4 cell counts, the frequency of resistance at ART failure was also higher than that observed in the early ART arm of HPTN 052 (70%–84% in 2 clinical cohort studies in sub-Sarahan Africa[20,21]; 50% in a randomized controlled clinical trial in the United States[22]). Many factors may have contributed to the lower rate of HIV drug resistance observed in the early ART arm of HPTN 052. In HPTN 052, participants in both study arms received adherence counseling and had quarterly viral load monitoring. Participants in the early ART arm may have been more likely to adhere to ART because they were taking ART primarily as an intervention to prevent partner infection, rather than for their own health.

Among participants in the early ART arm who failed ART, there was a strong association between higher baseline viral load and emergence of resistance at ART failure. This is consistent with results from an observational cohort study in Canada that reported an association of high baseline viral load and resistance at ART failure when ART was initiated at lower CD4 cell counts (median: 280 cells/mm^3).[23] Persons with higher baseline viral loads may have more diverse viral populations with a higher frequency of low-level drug-resistant variants or may have higher viral replication rates; these factors could favor emergence of resistant variants at ART failure. Of note, relatively few of the participants analyzed in this study had baseline resistance; therefore, further studies are needed to evaluate the clinical relevance of this association. We also found an association between educational level and resistance at ART failure. Further studies are needed to determine whether this reflects an association between educational level and ART adherence.

More than half of the participants who failed ART in this study never achieved viral suppression. There was no difference in resistance at ART failure among those who never achieved viral suppression, those who achieved viral suppression and remained suppressed until ART failure, and those who achieved viral suppression but had intermittent viremia before ART failure. Therefore, emergence of resistance at ART failure in this study does not seem to be driven by the selection of resistant variants after ART initiation, before viral suppression was established. This study reports resistance results in participants who failed ART by May 2011, when the interim study report was released (before participants were informed of the benefits of early ART for both the index and partner). Studies are underway to compare drug resistance in the early vs. delayed arms of the trial over the entire trial period and to assess the association of time to viral suppression, ART adherence (assessed through self-report, pill counts, and retrospective ARV drug testing), and drug resistance.

Emergence of HIV drug resistance in the setting of ART is concerning. Ongoing adherence counseling, frequent viral load monitoring, and prompt cessation of ART at ART failure (with a switch to a new regimen when feasible and appropriate) are likely to maximize the success of ART and reduce the risk of HIV drug resistance in both treatment and prevention settings.

ACKNOWLEDGMENTS

The authors thank the HPTN 052 study team and participants for providing the samples and data used in this study. The authors also thank the laboratory staff who helped with sample management and testing.

REFERENCES

1. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med.* 2011;365:493–505.
2. Cohen MS, Chen YQ, McCauley M, et al. Final results of the HPTN 052 randomized controlled trial: antiretroviral therapy prevents HIV transmission. Paper presented at: 8th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 19–22, 2015; Vancouver, Canada. Abstract: MOAC0101LB.
3. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis.* 2014;14:281–290.
4. The TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med.* 2015;373:808–822.
5. The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med.* 2015;373:795–807.
6. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med.* 2010;363:257–265.
7. Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents*. Department of Health and Human Services. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed August 17, 2015.
8. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. *JAMA*. 2012;308:387–402.
9. World Health Organization. *Guideline on When to Start Antiretroviral Therapy and on Pre-exposure Prophylaxis for HIV*. 2015. Available at: http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf?ua=1. Accessed October 6, 2015.
10. Uy J, Armon C, Buchacz K, et al. Initiation of HAART at higher CD4 cell counts is associated with a lower frequency of antiretroviral drug resistance mutations at virologic failure. *J Acquir Immune Defic Syndr.* 2009;51:450–453.
11. Lima VD, Reuter A, Harrigan PR, et al. Initiation of antiretroviral therapy at high CD4+ cell counts is associated with positive treatment outcomes. *AIDS.* 2015;29:1871–1882.
12. Lodi S, Phillips A, Fidler S, et al. Role of HIV infection duration and CD4 cell level at initiation of combination anti-retroviral therapy on risk of failure. *PLoS One*. 2013;8:e75608.
13. Fogel JM, Wang L, Parsons TL, et al. Undisclosed antiretroviral drug use in a multi-national clinical trial (HPTN 052). *J Infect Dis.* 2013;208:1624–1628.
14. Liu TF, Shafer RW. Web resources for HIV type 1 genotypic-resistance test interpretation. *Clin Infect Dis.* 2006;42:1608–1618.
15. Hollinger FB, Bremer JW, Myers LE, et al. Standardization of sensitive human immunodeficiency virus coculture procedures and establishment of a multicenter quality assurance program for the AIDS Clinical Trials Group. The NIH/NIAID/DAIDS/ACTG Virology Laboratories. *J Clin Microbiol.* 1992;30:1787–1794.
16. United Kingdom National External Quality Assessment Service (UK NEQAS). Available at: http://www.ukneqas.org.uk. Accessed September 12, 2015.

17. Hoen B, Bonnet F, Delaugerre C, et al. French 2013 guidelines for antiretroviral therapy of HIV-1 infection in adults. *J Int AIDS Soc.* 2014; 17:19034.
18. World Health Organization. *Maximizing the Treatment and Prevention Potential of Antiretroviral Drugs: Early Country Experiences towards Implementing a Treat-all Policy*. 2015. Available at: http://apps.who.int/iris/bitstream/10665/183599/1/WHO_HIV_2015.35_eng.pdf. Accessed September 12, 2015.
19. Kantor R, Smeaton L, Vardhanabhuti S, et al. Pretreatment HIV drug resistance and HIV-1 Subtype C are independently associated with virologic failure: results from the multinational PEARLS (ACTG A5175) clinical trial. *Clin Infect Dis*. 2015;60: 1541–1549.
20. Hamers RL, Sigaloff KC, Wensing AM, et al. Patterns of HIV-1 drug resistance after first-line antiretroviral therapy (ART) failure in 6 sub-Saharan African countries: implications for second-line ART strategies. *Clin Infect Dis.* 2012;54:1660–1669.
21. Marconi VC, Sunpath H, Lu Z, et al. Prevalence of HIV-1 drug resistance after failure of a first highly active antiretroviral therapy regimen in KwaZulu Natal, South Africa. *Clin Infect Dis.* 2008;46:1589–1597.
22. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Three- vs four-drug antiretroviral regimens for the initial treatment of HIV-1 infection: a randomized controlled trial. *JAMA*. 2006;296:769–781.
23. Harrigan PR, Hogg RS, Dong WW, et al. Predictors of HIV drug-resistance mutations in a large antiretroviral-naive cohort initiating triple antiretroviral therapy. *J Infect Dis.* 2005;191:339–347.